Palliative Radiotherapy for Advanced Cancers

Indications and Outcomes

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KEYWORDS

• Palliative radiotherapy • Palliative care • Supportive oncology • Radiation oncology

KEY POINTS

- Palliative radiotherapy is a safe, versatile, and effective therapy for various symptoms of advanced cancer.
- Indications for palliative radiotherapy are expanding from pure palliation to modifying the natural history of disease.
- A growing body of evidence supports the use of advance radiotherapy techniques in palliative radiotherapy.

INTRODUCTION

More than 40% of patients with metastatic cancer receive palliative radiotherapy (PRT).[1] PRT is an efficient, cost-effective, well-tolerated, and noninvasive treatment modality that can achieve rapid, durable symptom relief even for patients with poor prognosis.[2] Contemporary paradigms suggest a broader role for radiotherapy (RT) among patients with metastatic disease. Assessment of such patients requires recognition of symptoms and indications that may benefit from PRT. This review (1) defines the role of PRT as it relates to goals of care (GOC), (2) reviews common indications and evidence supporting PRT, and (3) reviews specific PRT options/considerations for common clinical scenarios.

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PATIENT SELECTION FRAMEWORK AND PROGNOSTICATION

Selecting appropriate PRT for a patient requires a multidisciplinary framework hinging on treatment intent. Historically, this was a binary choice between cure and symptom palliation, with the former typically delivered in 1.8- to 2.0-Gy daily fractions over 5 to 9 weeks. PRT regimens generally use hypofractionation (larger doses per fraction with fewer total fractions), balancing clinical efficacy against toxicity and logistical burden.

With advances in cancer care and the recognition of the oligometastatic state as a unique opportunity for long-term survival or potentially cure, defining treatment intent has become more nuanced. Clinicians now consider modifying disease trajectory and providing durable local tumor control in select patients with longer life expectancies. Treatment intent is influenced by factors such as prognosis, performance status, disease burden, radiosensitivity (**Table 1**),[3–7] alternative therapeutic options, potential toxicities, and patient priorities/values/goals.

Prognosis is notoriously challenging to predict with continual therapeutic advancements; physicians frequently overestimate survival of patients with advanced cancer.[8] Therefore, individualizing PRT courses on the sole basis of patient survival remains difficult. Nonetheless, prognostic models, such as TEACHH (*T*ype of cancer, *E*astern Cooperative Oncology Group performance status, *A*ge, prior palliative *C*hemotherapy, prior *H*ospitalizations, and *H*epatic metastases) and Chow's three variable number of risk factors[9] are valuable tools. Recent work to improve prognostication beyond traditional models for patients with symptomatic bone metastases has led to the creation of the Bone Metastases Ensemble Trees for Survival machine learning model, which uses 27 prognostic covariates to create patient-specific predicted survival curves.[10]

COMMON REASONS FOR CONSULTATION

Pain

Pain affects greater than 60% of patients with advanced cancers[11] caused by metastases, uncontrolled primary disease, or complications from therapy. RT can offer effective palliation of painful malignant lesions by reducing tumor size and modulating pain signaling pathways,[12] offering relief even if tumor response is minimal. Analgesia from PRT is best studied for bone metastases demonstrating response rates of greater than or equal to 60%,[13] but is also effective for other advanced cancers.

Clinicians should ensure medical management is optimized because one-third of patients' symptoms are inadequately controlled at baseline.[14] PRT may help de-escalate pain medications, but patients often benefit from continued use of opioids, adjuvants, and corticosteroids for pain optimization. Additionally, all patients with advanced cancers should be considered for palliative care consultation to ease

Table 1
Radiosensitivity of select histologies

Radiosensitive	Radioresistant
Lymphoma	Sarcoma
Myeloma	Renal cell carcinoma
Seminoma	Melanoma
Breast	Gastrointestinal
Prostate	

Data from Katsoulakis E, Kumar K, Laufer I, Yamada Y. Stereotactic Body Radiotherapy in the Treatment of Spinal Metastases. *Semin Radiat Oncol.* 2017;27(3):209-217.

pain and other physical and psychosocial symptoms known to potentiate physical and mental suffering.

Bleeding

Bleeding affects up to 10% of patients with advanced cancers[15] presenting as hemoptysis, hematemesis, hematochezia, hematuria, menorrhagia, or bleeding from fungating disease, and may require admission for urgent stabilization. Multidisciplinary management is necessary with medication management, systemic therapies, wound care, interventional procedures (surgery or embolization), and PRT all playing a potential role.

For patients stable enough for PRT, radiation can achieve hemostasis via tumor response, small vessel damage, and upregulation of the hemostatic cascade.[16,17] In some cases of advanced but curable disease, RT can temporize and stabilize before pursuing a more definitive treatment course.

Series suggest modest radiation doses can achieve hemostasis in up to 80% of patients, including primaries of the breast,[18] stomach,[19] cervix,[20] rectum,[21] prostate,[22] and skin,[23] among others. Our institution typically uses hypofractionated regimens with total doses 9 to 30 Gy in 3- to 10-Gy fractions with higher doses reserved for patients with good prognosis and few metastases.

Local Control

Local control, often studied in curative settings, is equally important in palliating advanced disease for patients with good prognosis. It is particularly important in the brain, spine, head and neck (H&N), and pelvis,[24] because loss of local control can result in severe morbidity and mortality, and present complicated, costly management challenges.

The most studied indications are metastatic cord compression and brain metastases (BM), but evidence supporting PRT for obstruction involving major airways, digestive/biliary tracts, major vessels, or genitourinary (GU) tract sites also exists. Clinical decision-making depends on harm-benefit assessment and multidisciplinary discussion, with prognosis and GOC informing recommendations.

PALLIATION OF PRIMARY SITES

Considerations for each disease site have led to focused research specific to histology and anatomic location. Herein we review data for managing advanced primary tumors of different sites. A summarized framework with treatment options and references follows in **Table 2**.

Head and Neck

PRT for cancers of the H&N offers a range of options from definitive management over 6 to 7 weeks to hypofractionated schedules, such as 0-7-21 or the Quad Shot regimen (3.7 Gy twice daily for four fractions repeated monthly up to three times). A recent review of treatment options offers the framework included in **Fig. 1**, which incorporates assessment of the patient, burden of disease, prior therapy, multidisciplinary discussion, toxicity risk, and GOC to inform decision-making.[25] This framework can be generalized to many primary sites.

Multiple trials conducted since 1993 have reported response rates ranging from 40% to greater than 80%, with even the shortest regimens (Quad Shot; 0-7-21) having response rates greater than 80%. In definitive treatment of H&N cancers 6 to 7 weeks of curative-intent concurrent chemoradiation can have significant side effects, but most trials in the palliative setting report toxicities in the range of less than or equal

Table 2
Treatment options for palliative radiotherapy of primary sites

Site	Prognosis	Regimen	Fractionation
Multiple	<4 mo		8 Gy/1 fx 20 Gy/5 fx 30 Gy/10 fx Supportive care only/hospice
Head and neck[25]	<4 mo 4–12 mo >12 mo	Quad Shot Porceddu Tata & Christie	14.8 Gy/4 fx BID (up to 3 cycles) 21 Gy/3 fx 30–32 Gy/5–8 fx 40–50 Gy/16 fx 60 Gy/20 fx 70 Gy/35 fx Chemoradiotherapy
Lung/thorax[26]	<4 mo 4–12 mo	Sundstrom	10 Gy/1 fx 17 Gy/2 fx (weekly) 30–40 Gy/10–15 fx 45 Gy/15 fx Chemoradiotherapy Intraluminal HDR brachytherapy
Breast[18]	All appropriate for short- or long-term prognosis patients	Rutgers UK FAST and Dragun UK FAST-Forward UK START Whelan	36.63 Gy/11 fx 30 Gy/5 fx 28.5 Gy/5 fx 27 Gy/5 fx 26 Gy/5 fx 40.05 Gy/15 fx 42.56 Gy/16 fx
Gastrointestinal (esophagus, stomach, colorectal cancers)	<4 mo 4–12 mo >12 mo	TROG 03.01	24 Gy/3 fx 30–35 Gy/10–15 fx 35 Gy/15 fx 50 Gy/25 fx Chemoradiotherapy Intraluminal HDR brachytherapy
Gynecologic (endometrial, cervical, vaginal cancers	<4 mo 4–12 mo >12 mo	Quad Shot 0-7-21	14.8 Gy/4 fx BID (up to 3 cycles) 7–8 Gy/1 fx on Day 0, 7, and 21 as needed 10 Gy/1 fx monthly up to 3 times 30 Gy/10 fx 50 Gy/20 fx HDR brachytherapy
Genitourinary (bladder cancer, prostate cancer)	<4 mo 4–12 mo >12 mo	Quad Shot MRC BA09	14.8 Gy/4 fx BID (up to 3 cycles) 21 Gy/3 fx delivered QOD 30–35 Gy/10 fx

(*continued on next page*)

Table 2
(*continued*)

Site	Prognosis	Regimen	Fractionation
			50–60 Gy/20–30 fx HDR brachytherapy
Extremity/bone	<4 mo 4–12 mo >12 mo		30 Gy/5 fx 30–40 Gy/10–15 fx 50 Gy/25 fx 66 Gy/33 fx
Skin	<4 mo 4–12 mo >12 mo	Princess Margaret	24 Gy/3 fx over 3 wk 30–35 Gy/5 fx over 3 wk 50 Gy/20 fx 55 Gy/20 fx 50–70 Gy/25–35 fx

Abbreviations: BID, twice daily fractionation; fx, fractions; HDR, high dose rate.

Data from Grewal AS, Jones J, Lin A. Palliative Radiation Therapy for Head and Neck Cancers. *Int J Radiat Oncol Biol Phys.* 2019;105(2):254-266.; Rodrigues G, Videtic GM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol.* 2011;1(2):60-71; and Grewal AS, Freedman GM, Jones JA, Taunk NK. Hypofractionated radiation therapy for durable palliative treatment of bleeding, fungating breast cancers. *Pract Radiat Oncol.* 2019;9(2).

to 30% to 40% grade 3, with less than 5% grade 4 and no grade 5 toxicity. Thus, PRT for advanced H&N cancers offers a reasonable probability of palliation at the cost of modest acute toxicity.

Thoracic

Advanced thoracic malignancies and lung metastases cause cough, hemoptysis, hematemesis, chest wall pain, dysphagia, odynophagia, or airway obstruction resulting in respiratory distress and/or postobstructive pneumonia requiring PRT.

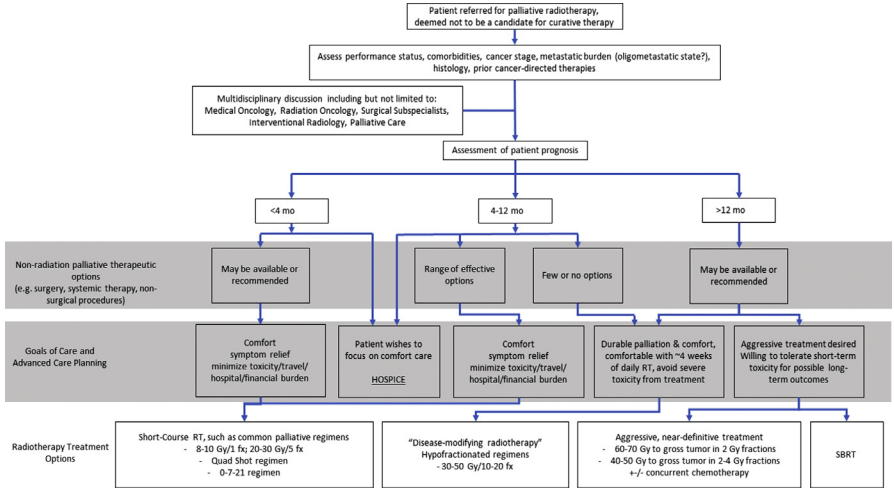

Fig. 1. Palliative RT framework. SBRT, stereotactic body radiotherapy. (*Adapted from* Grewal AS, Jones J, Lin A. Palliative Radiation Therapy for Head and Neck Cancers. Int J Radiat Oncol Biol Phys. 2019;105(2):254-266., with permission.)

PRT studies for non–small cell lung cancer (NSCLC) demonstrate the importance of prognosis for decision-making. Higher dose PRT regimens may improve survival or tumor control at the cost of treatment-related toxicity,[26] but a large systematic review found no survival difference when controlling for performance status.[27] Additionally, patients with stage III disease not amenable for curative-intent therapy should be considered for concurrent hypofractionated chemoradiotherapy if they have adequate performance status and life expectancy.[28] Depending on prognosis, traditional palliative regimens (20 Gy in 5 fractions or 30 Gy in 10 fractions) may be appropriate, whereas patients with longer survival may benefit from dose escalation to 45 to 50 Gy in 2.5- to 3-Gy fractions.

For patients with extensive stage small cell lung cancer, consolidative thoracic RT was shown to improve survival, but subsequent publications note discretion in patient selection is essential.[29] Patients with bulky mediastinal disease are at risk of complications and symptoms from local failure and may benefit from thoracic PRT. A 30 Gy in 10 fractions is well-tolerated in randomized clinical trials (RCTs) and an ideal palliative schedule for small cell lung cancer, but guidelines suggest higher doses may be appropriate for patients expected to have prolonged survival.

Breast

Presentation of advanced breast cancers can range from uncontrolled primary lesions resulting in pain, ulceration, or bleeding to advanced nodal disease of the axilla or low neck. Published PRT series include 30 Gy in 15 fractions[30] or 36.63 Gy in 11 fractions,[18] and slightly higher dose hypofractionated regimens offering low toxicities as would be used in definitive treatment paradigms. The literature notes the value of local control in these patients, because even those with advanced disease can live for many years. Radiobiologically, moderately hypofractionated PRT may offer the best possibility for durable local control.

Gastrointestinal

Advanced gastrointestinal tumors may cause obstruction, compression, pain, or bleeding. In esophageal cancer, dysphagia is relieved by external beam PRT, stent placement, endoscopic ablative treatment, or a combination thereof.

Esophageal stenting offers immediate relief and is recommended for patients with near-total obstruction or limited prognosis. However, tumor overgrowth compromises patency in approximately 12% of patients. Compared with stenting, PRT poses a lower risk of perforation, fistula, or hemorrhage while providing equivalent relief of dysphagia and greater relief of pain.[31] Additionally, PRT post-stenting improves dysphagia-free survival from 3 to 4 months.[32]

Common hypofractionated PRT regimens for dysphagia include 20 Gy in five fractions, 30 Gy in 10 fractions, and 35 Gy in 15 fractions.[33] Brief courses have been shown to be effective for greater than 50% of symptoms without grade 3 or higher toxicity.[34] Palliative chemotherapy may be incorporated with local PRT, although randomized evidence suggests similar dysphagia relief with increased toxicity.[33] Intraluminal brachytherapy (BT) also has high response rates (87%),[35] but if incorrectly performed can cause catastrophic consequences.

Biliary obstruction from cholangiocarcinoma often requires upfront stenting and can be followed by palliative external beam RT or intraluminal BT. In unresectable gastric cancer, PRT courses of 1 to 10 fractions are well tolerated and can alleviate bleeding, pyloric obstruction, and pain with response rates of 70% to 75% lasting 3 to 7 months.[36,37] Patients with rectal cancer not undergoing palliative resection can benefit from aggressive or short-course PRT (ie, 45–60 Gy in 25–30 fractions or 25–30 Gy in 5–6 fractions). Both

regimens provide comparable rates of pain relief, tumor control, and hemostasis (50%–80%) with median symptom recurrence at 5 months.[38] Concurrent chemoradiotherapy with fluorouracil is best for patients with good performance status and prognosis greater than 6 months.

Genitourinary

Advanced cancers arising from the GU system can cause hematuria, pain, recurrent urinary tract infections, urinary frequency, dysuria, erectile dysfunction, urinary retention or obstruction, hydronephrosis, or bowel obstruction. Hormonal therapy for prostate cancer and chemoimmunotherapy for bladder cancer are fundamental to the treatment and prevention of local symptoms. PRT can significantly lower rates of bleeding, pain, and obstruction.

Randomized evidence has demonstrated equivalent efficacy and toxicity between 21 Gy in three fractions and 35 Gy in 10 fractions for bladder cancer.[39] As seen in other disease sites, higher dose regimens did not translate into better palliation. In fact, prolonged PRT courses can inadvertently increase toxicity without benefit.[40] Patients with castration-resistant prostate cancer can similarly achieve palliation when treated to a total dose of 45 to 60 Gy in 2.0 to 2.5 Gy per fraction.[41]

Gynecologic

Advanced gynecologic tumors may cause vaginal bleeding, pain, dyspareunia, lymphedema, and compression of adjacent organs (gastrointestinal and GU). Hypofractionated PRT or BT can offer rapid hemostasis in locally advanced or recurrent cervical, endometrial, and vaginal cancers.[42]

A seminal study established the Quad Shot (3.7 Gy twice daily for four fractions repeated monthly up to three times) as a safe schedule highly effective for pain, bleeding, and obstipation.[43] The three-fraction course, 0-7-21, has also demonstrated excellent bleeding and pain control with low toxicity.[44] As in H&N cancers, these versatile regimens allow for evaluation of response and toxicity to guide decisions on total dose.

Because long- (ie, >5 fractions) and short-course PRT offer equal hemostasis and durability, short courses are preferable to reduce treatment burden and financial toxicity. These considerations are especially important in light of racial disparities in presentation, treatment, and outcomes between black and white women with endometrial and cervical cancer.[45,46]

Palliative options for locoregional recurrence from gynecologic malignancies depend on prior RT. For women without prior pelvic RT, curative intent external beam RT plus intracavitary/interstitial BT is recommended. For women with prior pelvic RT, reirradiation with external beam RT or incavitary/interstitial BT may be performed to small tumor volumes minimizing overlap. Alternatively, patients with prior incavitary/interstitial BT only may receive salvage surgery with intraoperative RT.[47] Pelvic exenteration is reserved as a last resort because of its significant morbidity.

Extremity, Bone, and Skin

By alleviating pain, bleeding, ulceration, lymphedema, and neurologic symptoms, PRT improves the quality of life in patients with skin cancers and sarcomas. Management of skin malignancies requires consideration of cosmetic and psychosocial outcomes in conjunction with tumor control. Fractionation schemes of 24 to 35 Gy in three to six fractions for basal and squamous cell carcinomas balance dose-related toxicity with response. For melanoma, larger fraction sizes (ie, $\geq$4 Gy per fraction to a total dose of >30 Gy) improve palliation and local control given its radioresistance.[23,48]

Advanced sarcomas often require systemic therapy with PRT delivered for local symptomatic relief. PRT is a recommended treatment option for palliation by the European Society of Medical Oncology[49] despite lack of robust data to guide optimal dose-fractionation. In a retrospective study of sarcomas treated with varying regimens (eg, 8 Gy in 1 fraction, 20 Gy in 5 fractions, 30–40 Gy in 10–15 fractions) PRT improved symptoms in 67% of patients.[50] Despite concerns over treatment-related morbidity, hypofractionated PRT and stereotactic body RT (SBRT) are promising choices for advanced sarcomas. Patients treated with 30 Gy in five fractions followed by immediate or delayed resection experience acceptable wound complications and reduction in treatment package time relative to conventional RT (50 Gy in 25 fractions) followed by delayed surgery.[51] With careful treatment planning, SBRT in recurrent sarcoma provides safe and effective local control and pain relief.[52]

PALLIATION OF METASTATIC SITES

Brain Metastases

BM may develop in up to 30% of patients with solid tumors[53] requiring special consideration given the potential for morbidity and neurologic death from uncontrolled intracranial progression. Treatment options include surgery, systemic therapy, and RT, alone or in combination.

Given the prognostic implications of BM, various systems have been developed to predict survival, including some specific for melanoma, NSCLC, and breast primaries.[54,55]

Early studies demonstrated survival benefit for surgery for solitary BM and improved local and/or whole brain control with the addition of RT (stereotactic radiosurgery [SRS] or whole-brain RT [WBRT]) postoperatively.[5,56] Surgery is preferred for rapid reversal of large and/or symptomatic BM and diagnosis for patients presenting with new metastatic disease.

Historically the role of systemic therapy for BM was limited by modest central nervous system penetration. Improved response rates from novel targeted/immune therapies (**Table 3**) raise the possibility of initiating systemic therapy early while periodically re-evaluating response.

RT has a well-defined role in the multidisciplinary management of BM. RT following surgery improves local and/or intracranial control and can prolong survival in patients

Table 3
Brain metastases systemic therapy response rates

Systemic Therapy (Target)	Response Rates (%)
Tyrosine kinase inhibitors (TKI)	
Gefitinib, erlotinib, afatinib (EGFR)	35–88
Osimertinib (EGFR)[73]	54–91
Ceritinib, alectinib, brigatinib (ALK)	35–68
Dabrafenib/vemurafenib (BRAF) ± trametinib (MEK)	18–90
Lapatinib (Her2) + capecitabine	6–66
Immunotherapy	
Pembrolizumab (PD-1)	26–33
Ipilimumab/nivolumab (CTLA4/PD-1)	6–55

Data from Han RH, Dunn GP, Chheda MG, Kim AH. The impact of systemic precision medicine and immunotherapy treatments on brain metastases. Oncotarget. 2019;10(62):6739-6753.

with limited disease. Nonsurgical series focus on the appropriate use of WBRT and SRS (alone or in combination) for management of BM. In general, a tradeoff exists between improved intracranial control of occult microscopic disease with WBRT and neurocognitive decline. Most evidence supports the use of SRS in patients with three or less BM with series demonstrating similar survival between approaches.[57,58] Emerging research examines SRS for more lesions, with older series suggesting total volume of disease treated rather than absolute number is an important predictor of survival.[59,60]

Additionally, although classic WBRT treatment fields are delivered with lateral opposed beams, newer techniques designed to spare the hippocampus from dose (hippocampal avoidance WBRT) have been explored to reduce neurocognitive decline. NRG CC001 was a phase III clinical trial that randomized 518 patients with nonhippocampal BM to standard WBRT with memantine or hippocampal avoidance WBRT with memantine (**Fig. 2**).[61] At 8 months, risk of cognitive failure (executive function, learning, memory) was significantly lower with hippocampal avoidance WBRT without overall survival (OS) differences. For many, this trial has established a new standard of care for patients without metastases in the hippocampal region.

Finally, a contemporary trial examining WBRT versus best supportive care in patients with BM from NSCLC showed no difference in survival and similar quality of life between treatment arms,[62] questioning the role of RT for patients with advanced NSCLC, BM, and short prognosis.

Bone Metastases

Solid tumors commonly metastasize to bone causing pain, pathologic fracture, or compression of nerve roots or the spinal cord. When incorporated into a multidisciplinary plan (eg, pain medication, systemic therapy, bone-modifying agents, surgical

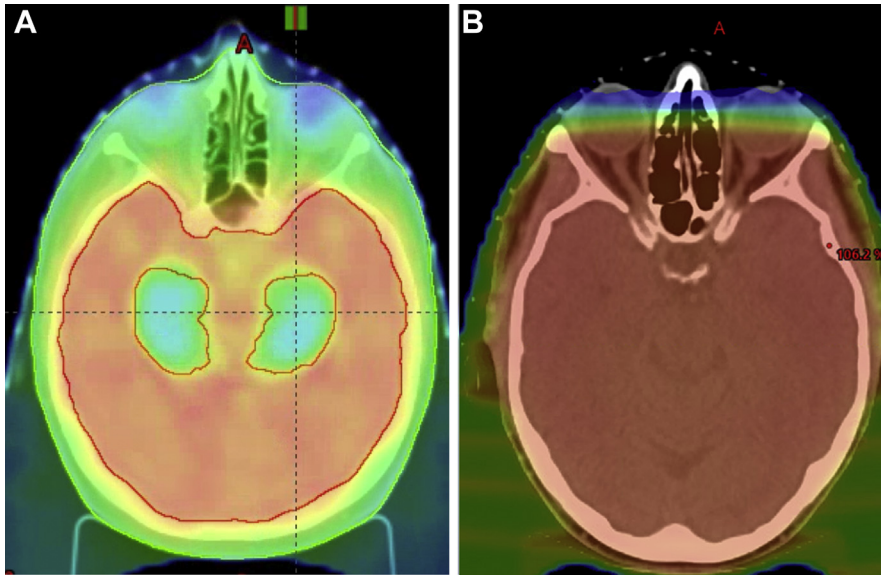

Fig. 2. (*A*) Conformally planned hippocampal avoidance WBRT spares hippocampi RT dose for patients without metastasis involving these regions. (*B*) Standard WBRT uses opposed lateral beams to treat the entire brain uniformly.

stabilization as needed), PRT is highly efficacious and well tolerated. In fact, 60% to 80% of patients experience partial pain relief and 30% to 50% experience complete pain relief within 3 to 4 weeks of starting PRT.[13]

In uncomplicated bone metastases (eg, lesions without a soft tissue component, impending fracture risk, spinal cord/nerve compression, or receipt of prior RT), pain control from single fraction RT is equivalent to longer regimens (ie, $\geq$5 fractions). Although retreatment rates are higher for single versus multifraction PRT, a single 8-Gy fraction is the preferred option for patients with poor prognosis.

However, multifraction PRT is appropriate for lesions following surgical fixation, with associated neuropathic pain, or with associated large soft tissue mass when local control is a secondary goal. If pain from an irradiated bone metastasis recurs or persists, repeat PRT can achieve 50% response rates.[63]

Spinal Cord Compression

Bone metastases of the vertebral column can result in spinal cord compression, which affects 2.5% to 5% of patients with cancer.[64] Cord compression can result in pain, spinal instability, and neurologic sequelae including paralysis, and multidisciplinary management may include neurosurgery, medical oncology, radiation oncology, orthopedics, or interventional radiology.

Medical management should include glucocorticoids to reduce edema contributing to symptoms, aggressive pain control, and consideration of systemic therapies. The NOMS (neurologic, oncologic, mechanical, systemic) Framework (**Table 4**) is used to create an appropriate multidisciplinary plan.

Postoperative radiation treatment is typically delivered over 2 weeks (30 Gy in 10 fractions), whereas patients receiving treatment without prior surgery may be given treatment over 1, 5, or 10 fractions.[65,66] For patients with radioresistant histology or recurrent disease that previously had conventional RT, advanced treatment with SBRT may be considered.

Table 4
Cord compression (NOMS) framework

NOMS Framework Component	Clinical Considerations	Treatment Options
*N*eurologic	Cord compression severity, presence of myelopathy	Radiosensitive and/or low-grade: treat with conventional RT alone
*O*ncologic	Radiosensitive vs radioresistant histology	Radioresistant and high-grade: separation surgery followed by SBRT
*M*echanical	Stable vs unstable spine	Unstable spine must always be managed before oncologic management, can be surgical or minimally invasive approach, consider RT approach following stabilization
*S*ystemic	Metastatic burden, life expectancy	For patients with short life expectancy, conventional RT only may be appropriate

Data from Katsoulakis E, Kumar K, Laufer I, Yamada Y. Stereotactic Body Radiotherapy in the Treatment of Spinal Metastases. Semin Radiat Oncol. 2017;27(3):209-217.

THE FUTURE OF PALLIATIVE RADIOTHERAPY

Disease-Modifying Radiotherapy: a New Category of Noncurative Intent

Historically, PRT was reserved for symptomatic disease sites but is now also considered for minimally symptomatic or asymptomatic sites with the goal of providing durable local control and/or modifying the natural history of disease. Recent data have shown patients with oligometastatic disease (<3–5 metastases) may benefit from prolonged survival following early local consolidative therapy (**Table 5**). The SABR-COMET trial demonstrated that in patients with controlled primary tumors and one to five oligometastases, SBRT to active disease sites improves OS by 22 months.[67] Confirmatory phase III trials are ongoing.

Irradiating the primary tumor alone in patients with low-burden metastases also seems to modify the clinical trajectory of various cancers. In the STAMPEDE trial, men with de novo low-burden metastatic prostate cancer receiving RT to the prostate had a 17% failure-free survival and 8% OS benefit within the first 3 years post-treatment with no increase in grade 3 toxicity.[68] In synchronous oligometastatic NSCLC, although no RCTs support treating the primary in isolation, a metanalysis of 668 patient showed that thoracic RT significantly improved OS.[69] In extensive stage small cell lung cancer in the preimmunotherapy era, palliative-dose RT to residual thoracic disease conferred a 3% to 13% OS benefit at 2 years.[70] Furthermore, the addition of aggressive locoregional radiation in chemoresponsive patients with de novo metastatic nasopharyngeal carcinoma improved survival from 55% to 76%.[71]

Advanced Technologies in Palliative Radiotherapy

Evolving diagnostic imaging, surgical techniques, and novel therapeutics are improving detection and survival for many cancers. Consequently, many patients with advanced disease are heavily pretreated, and radiation oncologists need to consider the use of advanced technologies to optimize tumor control and/or minimize toxicities. Principle among these technologies are intensity-modulated RT (IMRT), SBRT, and particle therapy.

IMRT is an advanced planning technique to generate treatment plans that conform closely to the edges of a target. It has been adopted as standard for definitive treatment of most primary tumors, whereas PRT often relies on simpler planning techniques that permit shorter treatment times and more reproducible patient positioning. However, IMRT may permit superior normal tissue sparing, potentially decreasing side effects, although this has yet to be confirmed in RCTs for many sites.

Another form of IMRT, SBRT precisely delivers “ablative” RT doses in five or fewer fractions to extracranial targets. Well-established for treatment of isolated lung, liver, or spine lesions, SBRT relies on advanced planning, targeting, and patient immobilization to deliver high doses and may be preferable in cases of limited metastatic disease, radioresistant histologies, or reirradiation.

Finally, although conventional RT relies on photons or electrons to deliver dose to target tissues, particle therapy uses heavy particles (protons, neutrons, or carbon ions) to treat tumor. In the United States proton therapy is the most widely available, with neutrons available at only a handful of sites, and carbon ions only in Europe and Asia. The theoretic advantage of particle therapy results from the physical nature of the beam delivery, whereby dose is deposited as the particle loses momentum, and no dose is delivered distal to the end of the particle’s range. This phenomenon results in sparing of tissues distal to the target, with some uncertainty (**Fig. 3**). Use of proton therapy for palliation has been published for H&N cancers,[72] but is otherwise limited. Appropriate clinical use of particle therapy requires experience, consideration of clinical risks/benefits, and potential financial implications of treatment.

Table 5
Summary of evidence supporting aggressive treatment of oligometastatic disease

Disease Site	Trial	Population	Intervention	Outcome
Prostate	STAMPEDE-RT[68]	Patients with metastatic hormone-sensitive prostate cancer (n = 2061)	SOC + prostate RT (55 Gy/20 fx or 36 Gy/6 fx) vs SOC	No OS benefit to the addition of prostate RT in unselect patients Improved OS from 73% vs 81% at 3 y in low-burden metastatic burden disease (as per CHAARTED trial)
Prostate	ORIOLE[74]	Patients with recurrent hormone-sensitive prostate cancer with 1–3 metastases (received no ADT within 6 mo of enrollment or 3 or more y total) (n = 54)	SBRT (19.5–48 Gy/3–5 fx) vs observation	mPFS not reached vs 5.8 mo (SBRT vs observation)
NSCLC	Gomez et al[75]	Patients with 3 or fewer metastatic lesions without progression after first-line systemic therapy (n = 99)	LCT (CRT/RT or surgery) ± maintenance therapy vs maintenance therapy alone or observation (no LCT)	Local progression 52% with LCT vs 70.8% in no LCT mPFS 11.9 mo vs 3.9 mo, 1 y PFS 48% vs 20% (consolidative vs maintenance)
NSCLC	Iyengar et al[76]	Oligometastatic patients with primary disease plus up to 5 metastases (n = 29)	SBRT + maintenance therapy vs maintenance therapy alone	PFS 9.7 mo vs 3.5 mo (SBRT + maintenance therapy vs maintenance therapy alone)
Nasopharynx	You et al[71]	Chemosensitive patients with de novo metastatic nasopharynx cancer (n = 126)	Chemotherapy + RT vs chemotherapy alone	OS 76.4% vs 54.5% at 2 y (chemotherapy + RT vs chemotherapy alone) PFS 35.0% vs 3.6% at 2 y
Mixed	SABR-COMET[77]	Patients with controlled primary Tumor and 1–5 metastatic lesions (93%–94% with 1–3 metastases) (n = 49)	SOC palliative treatment vs SOC + SBRT	mOS 41 mo vs 28 mo, mPFS 12.0 mo vs 6.0 mo (SOC vs SOC + SBRT)
Mixed	SABR-COMET-10[78]	Patients with controlled primary Tumor and 4–10 metastatic lesions (n = 159)	SOC palliative Treatment vs SOC + SBRT	Accruing, primary end point OS and secondary end points include PFS, time to new metastases, quality of life, and toxicity

Abbreviations: ADT, androgen-deprivation therapy; CRT, chemoradiotherapy; LCT, local consolidative therapy; mPFS, median progression-free survival; SOC, standard of care.

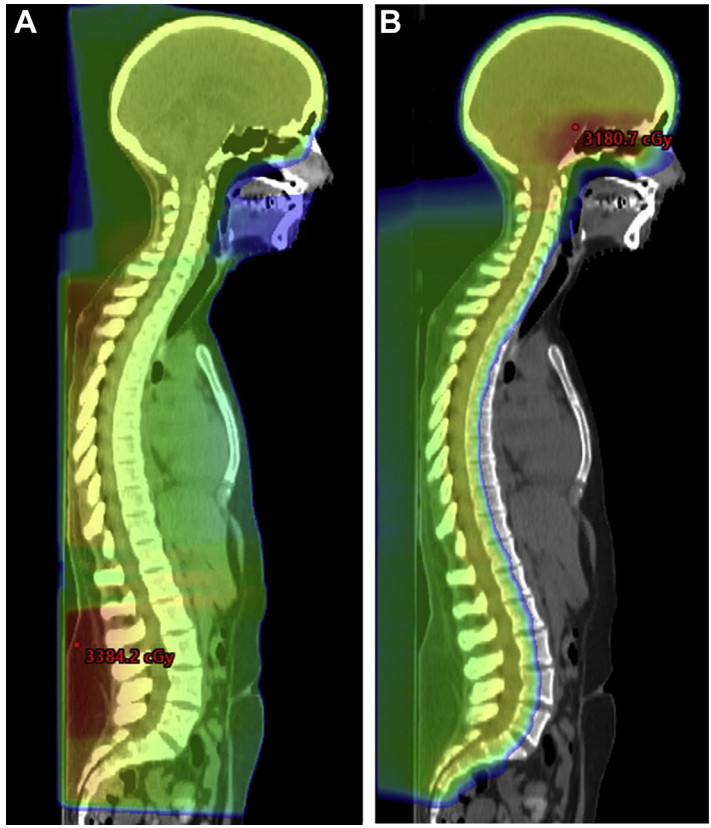

Fig. 3. Craniospinal dose distribution. (*A*) Photon versus proton photon craniospinal irradiation dose distribution. Note dose to anterior organs of the thorax and abdomen. (*B*) Proton craniospinal irradiation completely spares anterior structures.

SUMMARY

Many patients with advanced cancer benefit from PRT, and consultation with a radiation oncologist should be considered for any patient with pain, bleeding, local complications, or other tumor-related symptoms. Although multiple techniques and dose-fractionation schemes may be appropriate for a given clinical presentation, some common situations, such as BM, cord compression, bone metastases, and poorly controlled primary tumors, have published series or RCTs to support varied PRT regimens. Multidisciplinary discussion remains of utmost importance in deciding on an integrated treatment regimen. PRT may be an effective alternative to surgical management in cases where resection would be highly morbid, technically challenging, or not feasible.

CLINICS CARE POINTS

- Validated prognostic tools should be used for multidisciplinary decision-making for palliative radiotherapy (PRT).
- Advanced cancers of primary sites have many options for palliation ranging from single fraction to conventionally fractionated treatment over several weeks.

- Surgery should be considered for solitary or symptomatic brain metastasis. Whole-brain radiotherapy (WBRT) has been the standard management option for decades, but modern paradigms are expanding indications for use of stereotactic radiosurgery and hippocampal avoidance WBRT.
- Uncomplicated bone metastases are best treated with single-fraction PRT with response rates ranging from 60% to 80%. Patients requiring retreatment can have 50% response rates.
- Multiple models exist to guide management of metastatic epidural spinal cord compression. Patients managed with upfront surgery should receive postoperative radiation, whereas patients managed without surgery can be treated with 1, 5, or 10 fractions of PRT.
- Certain clinical scenarios may benefit from more aggressive palliative radiation for local control, which may be considered to be disease-modifying and palliative. Advanced technologies may be appropriate.

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